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**An intrinsic, label-free signal for identifying stem cell-derived cardiomyocyte subtype.**

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**Public Summary:**

Human-induced pluripotent stem cell (hiPSC)-derived cardiomyocytes have many promising applications, including the regeneration of injured heart muscles, cardiovascular disease modeling, and drug cardiotoxicity screening. Current differentiation protocols yield a heterogeneous cell population that includes pluripotent stem cells and different cardiac subtypes (pacemaking and contractile cells). The ability to purify these cells and obtain well-defined, controlled cell compositions is important for many downstream applications; however, there is currently no established and reliable method to identify hiPSC-derived cardiomyocytes and their subtypes. Here, we demonstrate that second harmonic generation (SHG) signals generated directly from the myosin rod bundles can be a label-free, intrinsic optical marker for identifying hiPSC-derived cardiomyocytes. A direct correlation between SHG signal intensity and cardiac subtype is observed, with pacemaker-like cells typically exhibiting ~70% less signal strength than atrial- and ventricular-like cardiomyocytes. These findings suggest that pacemaker-like cells can be separated from the heterogeneous population by choosing an SHG intensity threshold criteria. This work lays the foundation for developing an SHG-based high-throughput flow sorter for purifying hiPSC-derived cardiomyocytes and their subtypes.

**Scientific Abstract:**

Human-induced pluripotent stem cell (hiPSC)-derived cardiomyocytes have many promising applications, including the regeneration of injured heart muscles, cardiovascular disease modeling, and drug cardiotoxicity screening. Current differentiation protocols yield a heterogeneous cell population that includes pluripotent stem cells and different cardiac subtypes (pacemaking and contractile cells). The ability to purify these cells and obtain well-defined, controlled cell compositions is important for many downstream applications; however, there is currently no established and reliable method to identify hiPSC-derived cardiomyocytes and their subtypes. Here, we demonstrate that second harmonic generation (SHG) signals generated directly from the myosin rod bundles can be a label-free, intrinsic optical marker for identifying hiPSC-derived cardiomyocytes. A direct correlation between SHG signal intensity and cardiac subtype is observed, with pacemaker-like cells typically exhibiting ~70% less signal strength than atrial- and ventricular-like cardiomyocytes. These findings suggest that pacemaker-like cells can be separated from the heterogeneous population by choosing an SHG intensity threshold criteria. This work lays the foundation for developing an SHG-based high-throughput flow sorter for purifying hiPSC-derived cardiomyocytes and their subtypes.

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